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Evaluation of short-course radiotherapy followed by neoadjuvant bevacizumab, capecitabine and oxaliplatin and subsequent radical surgical treatment in primary stage IV rectal cancer

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Abstract

Background: To evaluate the efficacy and tolerability of preoperative short-course radiotherapy followed by capecitabine and oxaliplatin treatment in combination with bevacizumab and subsequent radical surgical treatment of all tumor sites in patients with stage IV rectal cancer.

Patients and methods: Adults with primary metastasized rectal cancer were enrolled. They received radiotherapy (5 x 5 Gy) followed by bevacizumab (7.5 mg/kg, day 1) and oxaliplatin (130 mg/m^2, day 1) intravenously and capecitabine (1000 mg/m^2 twice daily orally, days 1-14) for up to six cycles. Surgery was carried out 6-8 weeks after the last bevacizumab dose. The percentage of radical surgical treatment, 2-year survival and recurrence rates, and treatment-related toxicity was evaluated.

Results: Of 50 included patients, 42 (84%) had liver metastases, 5 (10%) had lung metastases, and 3 (6%) had both liver and lung metastases. Radical surgical treatment was possible in 36 (72%) patients. The 2-year overall survival rate was 80% [95% confidence interval (CI) 66.3-90.0%). The 2-year recurrence rate was 64% (95% CI, 49.8-84.5%). Toxic effects were tolerable. No treatment-related deaths occurred.

Conclusions: Radical surgical treatment of all tumor sites carried out after short-course radiotherapy, and bevacizumab-capecitabine-oxaliplatin combination therapy is a feasible and potentially curative approach in primary metastasized rectal cancer.

Introduction

Optimal treatment of patients with primary metastasized rectal cancer is controversial. Curative treatment would include resection of the primary tumor and all metastases, and many treatment options are available.

Most of the primary tumors are T3 (extending into the outer lining of the bowel or into adjacent tissue) or T4 (extending to the visceral peritoneum or other organs) rectal lesions with regional lymph nodes involved, and these tumors require downstaging before resection. Preoperative long-course radiotherapy is used with radiosensitizers, such as 5-fluorouracil, to downsize the primary tumor and reduce the risk of locoregional failure after resection [1, 2]. Nevertheless, 5-fluorouracil as a radiosensitizer has limited effects on systemic metastases. Systemic chemotherapy can be sequenced with chemoradiotherapy either before or after, but disadvantages include the extended period without systemic doses of chemotherapy and the additional acute toxicity of chemoradiotherapy when compared with radiotherapy alone. Furthermore, molecularly targeted agents that improved the survival of patients with advanced colorectal cancer are being tested as neoadjuvant therapy for rectal cancer [3-9].

Although there is limited evidence, the "liver first" approach has been proposed. It includes systemic chemotherapy followed by resection of liver metastases, and subsequent surgery for the primary rectal tumor [10]. This treatment sequence seems safe and effective, but it includes two surgical interventions and delayed treatment of the primary tumor.

To overcome the logistical problem of combining radiotherapy for primary rectal cancer with an adequate dose of systemic chemotherapy for metastatic disease, we propose a treatment sequence including preoperative short-course pelvic radiotherapy of five fractions of 5 Gy each (5 x 5 Gy), followed by capecitabine and oxaliplatin (CapeOx) given in combination with bevacizumab. Radical surgical treatment at all tumor sites is carried out 6-8 weeks after the last dose of bevacizumab. This short-course radiotherapy (5 x 5 Gy) has

comparable biological effective dose as a long-course regimen of 28 fractions of 1.8 Gy each (28 x 1.8 Gy) [11]. Furthermore, similar clinical outcomes have been shown when preoperative 5 x 5 Gy radiotherapy has been compared with 5-fluorouracil based 28 x 1.8 Gy chemoradiotherapy for T3 and T4 rectal carcinoma [12].

The purpose of the present study was to evaluate the efficacy and tolerability of this proposed regimen in a prospective, interventional, multicenter trial in patients with resectable primary metastasized rectal cancer in The Netherlands.

Patients and methods

Study design and end points

Between April 2006 and December 2010, 50 patients with primary metastasized rectal cancer were enrolled in seven centers in The Netherlands. This open-label, single-arm phase II clinical study was approved by the ethical committee of University Medical Center Groningen and registered with the Dutch health authorities (METc2005/270; NTR2029). All patients provided written informed consent. The primary endpoint was the percentage of patients receiving radical surgical treatment for all tumor sites (R0). Secondary endpoints were 2-year survival, 2-year recurrence rate, and treatment-related toxicity.

Eligibility criteria and pretreatment evaluation

Main inclusion criteria were age >18 years and histologically confirmed rectal adenocarcinoma, with resectable or ablatable metastases in the liver (total, ≤6 metastatic lesions in both lobes; lesions requiring ≤trisegmentectomy in either lobe; and adequate remaining vascular flow and biliary drainage) or lungs. Additional inclusion criteria were an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; adequate bone marrow function (white blood cell count ≥3.0 x 10^9/l; platelet count ≥100 x 10^9/l); adequate

hepatic function (serum bilirubin ≤1.5 mg/dl x upper normal limit; aspartate and alanine aminotransferase ≤1.5 mg/dl x upper normal limit); and adequate renal function (calculated creatinine clearance rate >50 ml/min, using Cockcroft-Gault formula).

Main exclusion criteria were extrahepatic or extrapulmonary metastases detected by clinical examination, computed tomography (CT) or fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET); previous pelvic radiotherapy; previous fluorouracil-based therapy for any malignancy; other concurrent chemotherapy; and the presence of or treatment for any malignancy other than non-melanoma skin cancer or in situ carcinoma of any organ within 5 years before the present study.

Baseline evaluation encompassed medical history, physical examination, laboratory tests, colonoscopy and rectal tumor biopsy. Baseline imaging of the primary tumor was with contrast-enhanced multidetector pelvic CT scan, and optionally magnetic resonance imaging (MRI). Liver and lung metastases were evaluated with abdominal and thoracic CT scans. Whole-body FDG-PET was done optionally to exclude extrahepatic and extrapulmonary metastases. Baseline imaging of the primary tumor and metastases were evaluated during the study by the investigators and retrospectively confirmed by an independent radiologist.

Preoperative treatment and clinical reassessment

Preoperative pelvic three-dimensional radiotherapy (total, 25 Gy; five fractions in 5 days) was delivered with an isocentric three- or four-field technique and mega-voltage radiation produced by a linear accelerator (Figure 1). The clinical target volume included the tumor, mesorectum, and internal iliac lymph nodes. Patients were positioned in either the supine or prone with a full bladder to decrease the volume of irradiated small bowel.

Systemic therapy was started within 2 weeks of completing radiotherapy. Patients were treated with six cycles of bevacizumab-CapeOx unless unacceptable toxicity occurred (Figure 1). On the first day of each cycle, bevacizumab (7.5 mg/kg, intravenous) and

oxaliplatin (130 mg/m^2, intravenous) were administered, each in a 2-h infusion. Capecitabine (1000 mg/m^2 twice daily, oral) was given during the first 2 weeks of each cycle. Radiological evaluation of the response of liver and lung metastases was carried out with contrast-enhanced multidetector CT scanning after two cycles of systemic therapy. If no progression was detected as assessed by RECIST criteria (version 1.0) [13], four additional cycles were administered.

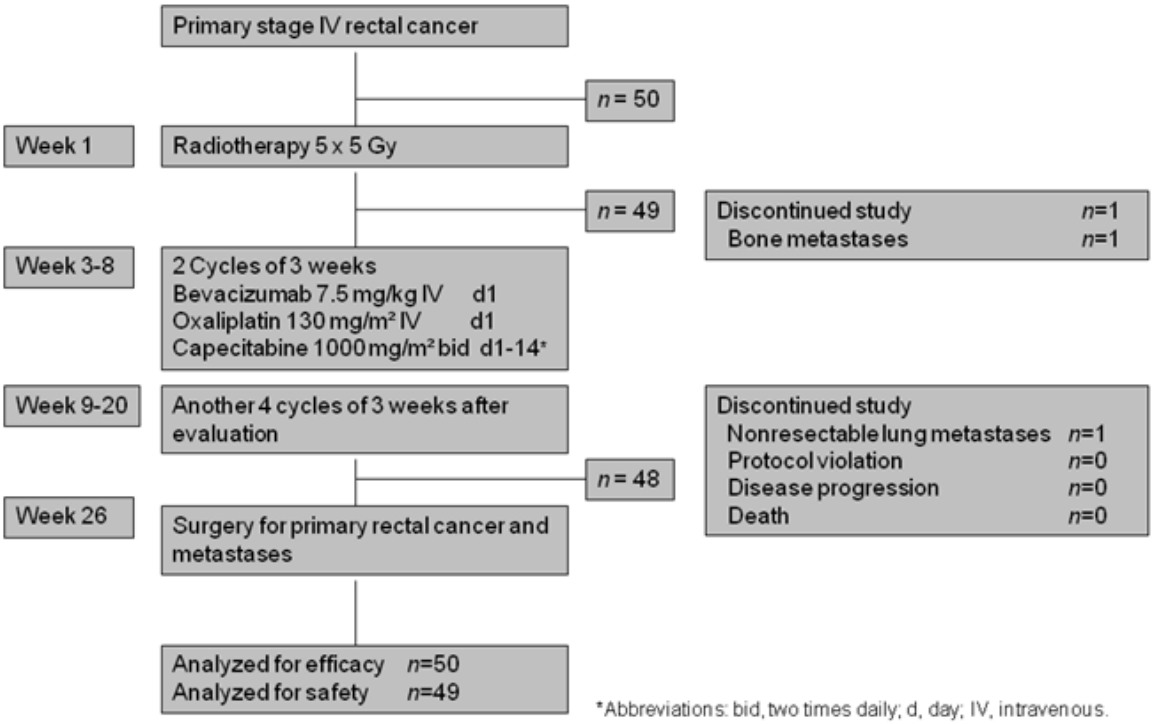
After completing preoperative treatment, patients were reassessed for resectability by clinical examination and CT, optionally MRI. Decision for surgery was made in each participating center by a multidisciplinary team.

Surgery and histopathologic evaluation

Surgical treatment was scheduled at 6-8 weeks after the last dose of bevacizumab. Optimal surgical resection of the primary tumor was carried out by total mesorectal excision (TME).The choice of surgical procedure was at the surgeon's discretion, such as diverting ileostomy after low anterior resection. Surgical treatment of metastases included partial liver or lung resection, radiofrequency ablation (RFA) of liver lesions, or a combination of resection and RFA; the procedure was selected in each study center according to local practice. Radiofrequency ablation was considered possible for lesions with largest diameter <30 mm.

Specimen dissection and mesorectum evaluation were carried out by the local pathologist as previously described [14]. Pathologic primary tumor response was assessed with Mandard's classification [15, 16]. Pathologic complete response after neoadjuvant treatment (ypCR) was defined as the absence of residual tumor cells in the primary tumor and lymph node specimens (ypT0N0). Downstaging was assessed by comparing pathologic stage (ypT) with baseline clinical T-stage. RFA was defined as radical (R0) if the 1-week post-procedural CT scan showed an ablation zone with tumor-free margins ≥5 mm.

Figure 1. Flowchart for the study of short-course radiotherapy followed by capecitabine and oxaliplatin in combination with bevacizumab and subsequent radical surgical treatment for patients with primary stage IV rectal cancer.



Toxicity and follow-up

Events related and unrelated to treatment were both evaluated. Toxic effects were categorized using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (available at: http://ctep.cancer.gov/reporting/ctc.html). Operative and postoperative complications were recorded on surgical postoperative forms. Patients treated with curative intent were evaluated according to the guidelines of the Dutch Association of Comprehensive Cancer Centers. No adjuvant chemotherapy was recommended after R0 resection.

Regular follow-up visits were performed every 3 months during the first 3 years and included clinical examination, serum carcinoembryonic antigen measurement, and CT or ultrasonographic imaging. Evaluation of ablation zones of liver metastases that had been treated with RFA was carried out as previously described [17]. In patients with recurrent disease, further treatment was done according to the local practice in each study center.

Statistical analysis

Sample size calculations were based on the two-stage design for phase II trials [18]. The minimal percentage of patients to achieve resectable disease after preoperative treatment was set at 30% [19]. A 50% R0 resection rate was targeted. It was calculated that 46 patients would be needed, with type I and type II errors each set at 10%. In the initial stage, 22 pre-planned patients were entered. After the pre-planned interim analysis showed R0 resections in 16 patients (>30%), the protocol was amended to include 24 additional patients. A total of 50 patients were included to compensate for potential losses caused by ineligible participants.

Overall survival for the intent-to-treat population was evaluated from the beginning of radiotherapy until death from any cause. Recurrence-free survival was calculated as the time from radical surgery to the diagnosis of the first distant or local recurrence. The 2-year

recurrence rate was calculated only for patients in whom radical surgical treatment was possible at all tumor sites. Overall survival rates in the intent-to-treat population and recurrence rates after radical surgical treatment were estimated using the Kaplan-Meier method. For statistical analyses GraphPad Prism (version 5.00 for Windows, GraphPad, La Jolla, California) was used.

Results

Patients and preoperative treatment

The intent-to-treat population consisted of all 50 patients. Demographic and baseline disease characteristics are presented in Table 1. All patients had an ECOG performance status of 0 or 1. The most commonly observed clinical stage was cT3N1-2 with liver metastases. Forty-two patients (84%) had liver metastases, 5 (10%) lung metastases, and 3 (6%) both liver and lung metastases. Eleven patients (22%) with obstructive bowel disease at presentation received a diverting colostomy.

Preoperative radiotherapy was given to all 50 patients and subsequent preoperative bevacizumab-CapeOx treatment was started in 49 patients (98%) (Table 2). One patient was withdrawn from the study because of bone metastases detected after radiotherapy. Most of the patients received six cycles of preoperative bevacizumab-CapeOx. No metastatic disease progression was reported by radiological reassessment after two cycles or completion of preoperative bevacizumab-CapeOx. There was one patient removed from the study because of irresectable lung metastases noted after completion of six cycles of preoperative bevacizumab-CapeOx. Median follow-up time was 32 months (95% CI, 29.4-38.7 months).

Efficacy

Forty-eight (96%) patients were scheduled for surgical treatment with curative intent. Radical surgical treatment at all tumor sites (R0) was possible for 36 (72%) patients (Table 3). There was no radiological evidence of progression after preoperative treatment, but irresectable disease was found at surgery in 8 of the 48 patients (17%). All liver and lung metastasectomies were considered microscopically radical. RFA was carried out in 11 patients (isolated treatment, 4 patients and combined with liver resection, 7 patients). CT scans at 1 week after ablation showed adequate margins in all lesions that had been treated with RFA.

Of the 48 patients scheduled for curative surgery, the primary rectal tumor was resected in 43 (90%) individuals (Table 3). Simultaneous TME and surgical treatment of metastases was carried out in 26 patients. In seven patients, surgery for metastases was carried out first, followed by TME in five patients at a later time. In 12 patients, the primary tumor was resected before surgical treatment of the metastases. In four patients, the rectal resection margins showed tumor cells microscopically (R1). The initial stages of the primary tumor in these four patients were T3N2 (n = 2), T3N1 (n = 1) and T4N1 (n = 1).

A complete pathologic response of the primary rectal tumor (ypCR) was reported in 11 of 43 patients (26%), and a near-complete response (ypNCR; only a few residual tumor cells present) in 7 (16%) (Table 3). Local tumor (ypT) downstaging was documented in 20 (47%) patients who had rectal tumor resection (supplementary Table S1).

The 2-year overall survival rate was 80% (40 of 50 patients; 95% CI, 66.3 to 90.0%) in the intent-to-treat group (Table 3 and Figure 2). The 2-year recurrence rate was 64% (23 of 36 patients; 95% CI, 49.8 to 84.5%) after R0 resection. Median time to recurrence was 13

Table 1. Baseline patient characteristics.

Characteristic		Results[a] (*n* = 50)
Sex		
	Men	27 (54)
	Women	23 (46)
Age (y)		
	Median	59
	Range	(35-75)
Clinical tumor category		
	T2N0	0 (0)
	T2N1	4 (8)
	T3N0	6 (12)
	T3N1-2	32 (64)
	Substaging[b]	
	T3a (< 1mm)	7 (14)
	T3b (1 to 5 mm)	23 (46)
	T3c (5 to 15 mm)	8 (18)
	T4N0	1 (2)
	T4N1-2	7 (14)
	Perforation into visceral peritoneum	4 (8)
	Invasion of other organs	3 (6)
	T3-4N2	13 (26)
Tumor localization		
	Low (0 to 5 cm)	23 (46)
	Middle (5 to 10 cm)	21 (42)
	High (10 to 15 cm)	6 (12)
Metastatic site		
	Liver	42 (84)
	Lung	5 (10)
	Lung and liver	3 (6)
Liver metastases		
	Unilobar	21 (47)
	Bilobar	24 (53)
	1 to 3	36 (72)
	> 3	9 (18)
Lung metastases		
	1	5 (10)
	>1	3 (6)

[a] Results shown as *n* (%) unless otherwise indicated.
[b] Distance to the endopelvic fascia.

Table 2. Summary of patient exposure to study drugs.

Drug exposure	**Results[a] (*n* = 50)**	
Bevacizumab-capecitabine-oxaliplatin[b]	49	(98)
Chemotherapy duration (week), median (range)	18	(3-20)
Cycles[c]		
Cycles started, median (range)	6	(1-6)
Patients receiving six cycles	42	(84)
Patients with 1 week delay during cycles	10	(20)
Patients with 2 weeks delay during cycles	2	(4)
Patients with 20% dose reduction		
Bevacizumab	1	(2)
Capecitabine	4	(8)
Oxaliplatin	2	(4)
Patients with drug discontinuation		
Bevacizumab	3	(6)
Capecitabine	1	(2)
Oxaliplatin	1	(2)

[a] Results shown as *n* (%) unless otherwise indicated.
[b] One patient was discontinued from the study because of bone metastases noted after radiotherapy.
[c] Cycle duration, 21 days.

months (range 7-20 months). Curative treatment of recurrent disease was possible in 13 of the 23 patients (57%). Local pelvic relapse occurred in two patients—at 5 and 15 months after surgery for the primary tumor. One of these patients subsequently had an abdominoperineal resection with curative intent.

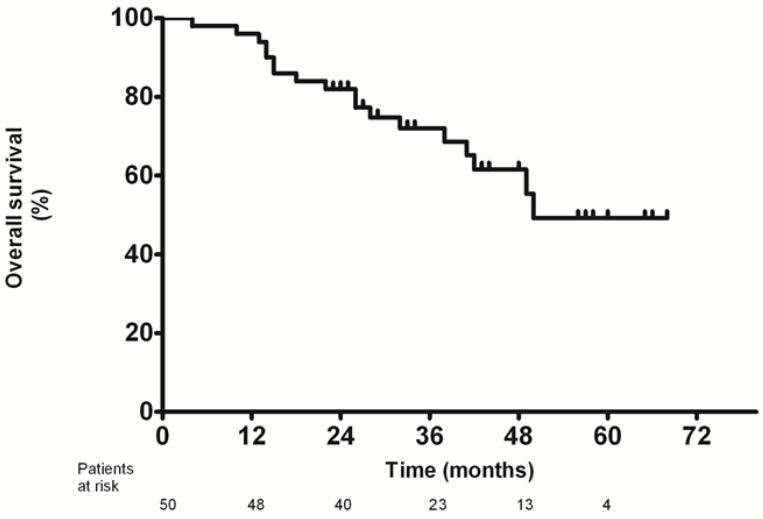


Figure 2. Overall survival rate of patients in the intent-to-treat group, with numbers of patients at risk, through 6 years.

Safety and compliance

There were no grade 3-4 adverse events during or after preoperative radiotherapy in all 50 enrolled patients (Table 4). In 38 (76%) patients, bevacizumab-CapeOx treatment was initiated as planned within 2 weeks after radiotherapy. In seven (14%) patients, there was a delay of 1 week because of grade 2 radiotherapy-related toxicity (proctitis, diarrhea, pain). A more than 1-week delay (range 1-6 weeks) occurred in four (8%) patients, caused by ileus (one patient) or logistical reasons (three patients). In 42 (84%) patients, all six cycles of bevacizumab-CapeOx treatment were administered. The most common non-surgical grade ≥3 toxic effects were diarrhea and pulmonary embolisms (Table 4). The most frequent grade 1-2

adverse reactions to bevacizumab-CapeOx treatment were fatigue, sensory neuropathy, and nausea (supplementary Table S2).

Median time between completion of neoadjuvant treatment and surgery was 39 (range 17-205; interquartile range 36-50) days. Median hospitalization time was 8 (range 6-135) days in patients who had TME alone , and 13.5 (range 6-65) days in patients who had simultaneous TME and metastases surgery. The most frequent postoperative complications within 60 days after surgery were wound and abdominal cavity infections (nine patients; Table 4 and supplementary Table S3). No patient died within 90 days after surgery.

Discussion

The present results support the hypothesis that short-course radiotherapy followed by bevacizumab-CapeOx combination therapy is an effective preoperative treatment for patients with primary metastasized rectal cancer. Subsequent radical surgical treatment at all sites (R0) was achieved in 72% of the 50 patients (Table 3).

There are few data about resection rates in patients who initially present with metastases to the liver and lungs. A strong relation had been reported between response to chemotherapy and subsequent resection rate of metastatic disease [20], but those findings were primarily for initially irresectable metastatic disease [21, 22]. In the present study, short-course radiotherapy followed by bevacizumab-CapeOx treatment provided good control of the primary rectal tumor before surgery; progression of the rectal tumor was not observed during the interval between the start of radiation therapy and surgery (median 180 days, range 132-360). This treatment scheme yielded a pathologic complete response of the primary tumor in 26% of patients and a pathologic near-complete response in 16% of patients (Table 3). These response frequencies are comparable or better than those with other neoadjuvant chemoradiation schemes, that have pathologic complete response from 10% to 30 % in patients with locally advanced rectal cancer [3-9, 23-25]. The schedule and doses of

Table 3. Surgical procedures and efficacy results.

Characteristic	Results[a] (*n* = 50)		Total *n*
Patients who had surgery with curative intent			48
Radical operation at all tumor sites (R0)			36
Retum			
Hartmann procedure	19	(53)	
Abdominoperineal resection	11	(30)	
Low anterior resection	6	(17)	
Metastases			
Liver resection	8	(22)	
Liver resection (> 3 segments)	11	(30)	
Liver resection and radiofrequency ablation	7	(20)	
Radiofrequency ablation alone	4	(11)	
Lung resection	5	(14)	
Liver and lung resection	1	(3)	
Primary rectal tumor resection[b]			43
Resection type			
R0 resection of primary tumor[c]	39	(91)	
R1 resection of primary tumor	4	(9)	
Response			
Pathologic complete response	11	(26)	
Pathologic near-complete response	7	(16)	
Nonradical treatment/irresectable disease			14
R1 resection rectum			
Tumor at circumferential resection margin	3	(21)	
Tumor at distal resection plane	1	(7)	
Incurable/irresectable disease			
Peritoneal carcinomatosis	2	(14)	
Liver metastases	5	(37)	
Lung and liver metastases	1	(7)	
Incurable disease before surgery	2	(14)	
Results of treatment			
Overall			50
2-year overall survival[d]	40	(80)	
After R0			36
2-year recurrence rate after R0[e]	23	(64)	
Local recurrence, rectum, after R0	2	(6)	
Distant recurrence after R0	21	(58)	
Liver	10	(28)	
Lung	7	(19)	
Liver and lung	2	(6)	
Other/diffuse	2	(6)	

[a] Results shown as *n* (%) unless otherwise indicated.
[b] Forty-three primary rectal tumors resected; 39 R0 and 4 R1. Three patients with R0 rectal tumor resection were not resected for metastases.
[c] R0: radical resection with >1mm margin in the resected tumor; R1: microscopic tumor at the resection margin.
[d] Forty of 50 patients (80%); 95% confidence interval, 66% to 90%.
[e] Twenty-three of 36 patients (64%); 95% confidence interval, 50% to 84.5%.

Table 4. Toxicity and treatment compliance.

Variable	Patients exposed to treatment, *n*	Total *n*
Grade 3 to 4 toxicity (radiotherapy)	0	50
Timing of initiating bevacizumab and CapeOx[a]		49
As planned, within 2 weeks after radiotherapy	38	
Delayed 1 week because of grade 2 toxicity[b]	7	
Delay > 1 week[c]	4	
Compliance bevacizumab and CapeOx		49
6 cycles	42	
4 cycles	3	
3 cycles	3	
1 cycle	1	
Grade 3 to 4 toxicity bevacizumab and CapeOx	19	49
Gastrointestinal	6	
Vascular	6	
Pain (tumor)	4	
Dermatologic	1	
Infection	1	
Other	1	
Surgical complications within 60 days after surgery		48
Infection / abscess	12	
Wound	6	
Abdominal cavity	3	
Perineal	2	
Thorax	1	
Anastomotic leak	1	
Rectal stump leak	1	
Bleeding	1	
Death	0	
Reoperation		48
1	4	
≥ 2	6	
Radiological intervention	5	

[a] CapeOx: capecitabine and oxaliplatin.

[b] Proctitis, diarrhea, and pain.

[c] Delay >1 week (range, 1-6 weeks): logistical reasons, three patients; necessity of colostomy because of unforeseen obstruction, one patient.

bevacizumab-CapeOx used in the present study may have contributed to the high response frequencies. The present findings are substantiated by results of trials that report pathologic complete response as an early prognostic marker of better disease-free survival [26, 27].

Neoadjuvant long-course chemoradiotherapy, with surgery planned 6-10 weeks later, has been recommended for patients with locally advanced (T3 or T4) rectal cancer. In the present study, there was a 47% primary rectal tumor downstaging from clinical to pathologic stage (supplementary Table S1), consistent with results from preoperative long-course [28, 29] and short-course regimens for locally advanced rectal cancer [30-33].

RFA was used in 11 patients in the present trial as adjunct or single treatment of metastases (Table 3). This procedure has not been well studied for liver metastases from rectal cancer, and no randomized controlled trials have been reported [34]. Local recurrence rates are not significantly different after RFA than anatomic or wedge resections of the liver metastases <30 mm [35, 36]. In the present study all metastatic lesions treated with RFA were <17 mm.

A main finding of this study is the high tolerability of the regimen, with 84% of the patients completing radiotherapy and systemic treatment without major delay (Table 2). The safety profile of preoperative bevacizumab-CapeOx treatment after short-course radiotherapy is comparable with that reported in other studies, with diarrhea, hand-foot syndrome, and thromboembolic events among the most common adverse events [37]. Surgery-related morbidity occurred mainly from infection (supplementary Table S3). Postoperative complications may occur after major pelvic surgery, especially when bevacizumab is added to neoadjuvant chemoradiotherapy [37-40]. Surgery-related morbidity we report does not exceed morbidity reported in these studies. The frequency of surgical intervention for these complications in this study was relatively high. Persistent abdominal infections led in a few patients to frequent interventions. We were not able to attribute toxicity to a specific drug or

modality with certainty. A Hartmann procedure was chosen over immediate anastomosis in 19 patients to avoid possible anastomotic complications that could delay further treatment.

The 2-year overall survival rate in the present study (80%) (Table 3) is comparable to published results for patients with disease of similar severity [41, 42]. There were 23 (64%) patients that had recurrent disease within 2 years after radical surgical treatment. In the present study, most recurrences were in the liver, and only two patients had local pelvic relapse. Patterns of recurrence have not been well documented in patients with primary metastasized rectal cancer who undergone complete resection. Recurrences may involve distant sites, rather than the local pelvic sites [43], but most studies included patients with both colon and rectal cancer in the same analysis [44, 45].

A potential shortcoming of the present and similar studies is the definition of resectable metastatic disease before treatment. In daily clinical practice, it may be difficult to determine resectability of metastases. In the present study, assessment of the resectability of metastatic disease was based on leaving a functional remnant of the noninvolved organ. This assessment may be inherently subjective [46]. Despite good response and absence of clinical and radiological progression during preoperative treatment, 10 of the present patients eventually had irresectable disease.

In conclusion, short-course radiotherapy followed by preoperative bevacizumab-CapeOx treatment may be a feasible and potentially curative approach for primary metastasized rectal cancer. This approach may enable treatment of metastatic disease and good control of the primary rectal tumor. The present study is the basis of the experimental arm of the RAPIDO study (NCT01558921; 5 x 5 Gy/ CapeOx/surgery versus long-course chemoradiotherapy/surgery), which has a primary end point to evaluate 3-year disease-free survival in patients with locally advanced rectal cancer without metastatic disease.

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Disclosure

The authors have declared no conflicts of interest.

Supplemental data

Supplementary Table S1. Downstaging of primary rectal cancer.

		Initial imaging of rectal cancer[a]			
		All[b]	T2	T3	T4
		(*n* = 43)	(*n* = 4)	(*n* = 32)	(*n* = 7)
Pathologic staging after surgery					
	ypT0	11 (26)	1 (25)	8 (25)	2 (29)
	ypT1	0 (0)	0 (0)	0 (0)	0 (0)
	ypT2	8 (18)	2 (50)	5 (16)	1 (14)
	ypT3	22 (51)	1 (25)	18 (56)	3 (43)
	ypT4	2 (5)	0 (0)	1 (3)	1 (14)
T downstaging		20 (47)	1 (25)	13 (41)	6 (86)
T progression		2 (5)	1 (25)	1 (3)	0 (0)

[a] Results shown as *n* (%) unless otherwise indicated.
[b] Forty-three primary rectal tumors resected: 39 R0 and 4 R1; 3 patients with radical operation rectal tumor resection did not have resection of metastases.

Supplementary Table S2. **Preoperative treatment-related grade 1 to 2 toxicity.**

Toxic effect[a]		***n* (%)**[b]
Gastrointestinal		
	Nausea	17 (34)
	Vomiting	9 (18)
	Constipation	7 (14)
	Diarrhea	7 (14)
	Anorexia	3 (6)
	Mucositis	1 (2)
Constitutional		
	Fatigue	27 (54)
	Weight loss	3 (6)
	Fever	2 (4)
Dermatologic		
	Phlebitis	8 (16)
	Hand-foot syndrome	6 (12)
	Extravasation	4 (8)
Infection		
	Urinary tract	2 (4)
	Lung	1 (2)
	Gallbladder	1 (2)
	Other	2 (4)
Pain		
	Abdominal	5 (10)
	Tumor	4 (8)
Neurologic		
	Sensory neuropathy	26 (52)
	Dizziness	1 (2)
Cardiac		
	Hypertension	4 (8)
	Ischemia	0 (0)
Vascular		
	Embolus	1 (2)
	Vasculitis	1 (2)
Allergic reaction		5 (10)
Bleeding		4 (8)
Other		7 (14)

[a] Toxic effects were categorized using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.
[b] Results shown as *n* (%) unless otherwise indicated.

Supplementary Table S3. Surgical complications.

60 day surgical complications		TME[a] alone	TME simultaneous with treatment of metastases	Treatment of metastases without TME
Infection / abscess				
	Wound	1	5	0
	Abdominal cavity	2	1	1
	Perineum	1	1	0
	Thorax	0	1	0
Anastomotic leak		0	1	0
Rectal stump leak		0	1	0
Bleeding		0	1	0
Reoperation				
	1 operation	2	2	0
	≥2 operations	2	4	0
Radiological intervention		2	2	1
Death		0	0	0
Hospital stay (d)		8 (6-135)	13.5 (6-64)	6.5 (3-12)

[a] TME, total mesorectal excision

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